



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/57 // (A61K 31/57 A61K 31:165)		A1	(11) International Publication Number: WO 93/11773 (43) International Publication Date: 24 June 1993 (24.06.93)
<p>(21) International Application Number: PCT/EP92/02826</p> <p>(22) International Filing Date: 7 December 1992 (07.12.92)</p> <p>(30) Priority data: 91311761.0 18 December 1991 (18.12.91) SE</p> <p>(71) Applicant: AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE).</p> <p>(72) Inventors: CARLING, Christer, Carl, Gustav ; Backvägen 8, S-240 10 Dalby (SE). TROFAST, Jan, William ; Väpenkroken 34, S-226 47 Lund (SE).</p> <p>(74) Agents: HJERTMAN, Ivan et al.; AB Astra, Patent Department, S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: NEW COMBINATION OF FORMOTEROL AND BUDESONIDE

(57) Abstract

Effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are used in combination for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam

New combination of formoterol and budesonide.

5

Field of the invention

This invention relates to improvements in the treatment of mild as well as severe asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator in combination with a steroid anti-inflamatory drug for the treatment of respiratory disorders such as asthma, and to pharmaceutical compositions containing the two active ingredients. It emphasizes the use of a long-acting bronchodilator which provides rapid relief of symptoms.

Background of the invention

20 There have recently been significant advances in our understanding of asthma. Despite many advances, both in awareness of the disease by doctors and patients alike, coupled with the introduction of very powerful and effective anti-asthma drugs, asthma remains a poorly understood and often poorly treated disease. Previously, contraction of airway smooth muscles has been regarded as the most important feature of asthma. Recently there has been a marked change in the way asthma is managed, stemming from the fact that asthma is recognized as a 25 chronic inflammatory disease. Uncontrolled airway inflammation may lead to mucosal damage and structural changes giving irreversible narrowing of the airways and fibrosis of the lung tissue. Therapy should therefore be aimed at controlling symptoms so that normal life is 30 35 possible and at the same time provide basis for treating

the underlying inflammation.

The most common cause for poor control of asthma is poor compliance with the long-term management of chronic 5 asthma, particularly with prophylactic treatments, such as inhaled steroids, which do not give immediate symptom relief. Patients will readily take β_2 -agonist inhalers, since these provide rapid relief of symptoms, but often do not take prophylactic therapy, such as inhaled 10 steroids, regularly because there is no immediate symptomatic benefit. They also counteract down regulation of β_2 -adrenoceptor agonists.

Formoterol, (N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl)formamide), is an adrenóceptor agonist which selectively stimulates β_2 -receptors, thus producing relaxation of bronchial smooth muscle, inhibition of the release of endogenous spasmogens, inhibition of oedema caused by 20 endogenous mediators, and increased mucociliary clearance. Inhaled formoterol fumarate acts rapidly, usually within minutes which gives the patient immediate confirmation that he has taken an adequat dose and thereby avoiding overdosing of both β -agonist and 25 steroid. Inhaled formoterol also exerts a prolonged bronchodilation, which in clinical trials has been demonstrated as up to 12 hours.

Budesonide, (16,17-butylidenebis(oxy)-11,21-dihydroxypregna-1,4-diene-3,20-dione), may be given in a 30 high inhaled dose (up to 2 mg daily) with very low systemic effects, possibly because of its rapid metabolism. The high rapid systemic elimination of budesonide is due to extensive and rapid hepatic 35 metabolism. Long term clinical studies have shown that inhaled budesonide is a pharmacologically safe drug. High doses of inhaled budesonide are highly effective and well

tolerated when used in oral steroid replacement therapy. Budesonide represents a logical safe and effective therapy for long term control of asthma.

5 The inhaled route of administration enables the dose to be delivered directly to the airways. By this type of administration, it is possible to give a small dose and thereby minimizing unwanted side-effects. The drawbacks of the currently available bronchodilators are their
10 relatively short duration of action. By using a compound with long duration e.g. formoterol it would be possible to avoid the nocturnal asthma, which so often causes considerable anxiety and debility to the patients.
Formoterol gives less nocturnal waking than the commonly
15 used short-acting agonists like salbutamol, terbutaline and the like. Formoterol has been registered for oral administration in Japan since 1986.

20 Pharmaceutical combinations of long-acting β_2 -agonists and steroids are disclosed in two European applications, EP 416950 which discloses the combination of salmeterol and beclomethasone, and EP 416951 which discloses the combination of salmeterol and fluticasone propionate.

25 In Ann. Allergy 1989, 63 (3), p. 220-224 the use of a β_2 -agonist, i.e. formoterol and a steroid, i.e. budesonide separately are mentioned. It is not disclosed a pharmaceutical combination including both formoterol and budesonide, or the use of the two compounds in
30 combination therapy. The use of a β_2 -agonist and a steroid separately is also mentioned in Lung (1990), 168, no. supp, p. 105-110.

Outline of the Invention

35 The present invention is based on the concept of a novel combination therapy whereby formoterol (and/or a

physiologically acceptable salt and/or solvate thereof) and budesonide are administrated simultaneously, sequentially or separately by inhalation. This combination has not only a greater efficiency and duration of bronchodilator action but the combination also has a rapid onset of action. This new feature is of utmost importance in order to establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers. This simplifies life for patients considerably and makes life more comfortable and secure. The rapid onset of the long-acting β_2 -agonist gives the patient immediate confirmation that he has taken an adequate dose and thereby avoiding overdosing of both β_2 -agonist and steroid. Since the use of formoterol instead of salmoterol gives a much more rapid onset the combinations according to the invention have a number of advantages compared to the combinations disclosed in EP 416950 and EP 41651. The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma.

The present invention provides a medicament containing, separately, or together, (i) formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and (ii) budesonide for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.

The invention also provides a pharmaceutical composition for administration by inhalation in the treatment of respiratory disorder which composition comprises formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

According to another aspect of the invention there are provided pharmaceutical compositions comprising effective

amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.

The invention further provides formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide for use in combination therapy by simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.

Further the invention provides the use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) in the manufacture of a medicament for combination therapy where formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorder and the use of budesonide in the manufacture of a medicament for combination therapy where formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorder.

The invention additionally relates to the use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide in the manufacture of a medicament for combination therapy for simultaneous, sequential or separate administration of formoterol and budesonide by inhalation in the treatment of respiratory disorder.

According to a further feature of the invention there is provided a method of treating respiratory disorder which comprises the simultaneous, sequential or separate

administration by inhalation of effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

- 5 Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids, such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalenecarboxylate or oleate. Formoterol is preferably used in the form of its fumarate salt and as a dihydrate.
- 10
- 15

The ratio of formoterol to budesonide used according to the invention is preferably within the range of 1:4 to 1:70. The two drugs may be administered separately in the same ratio.

20

The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 6 to 100 µg with a preferred dose of 6-48 µg and the suitable daily dose for budesonide is 50 to 4800 µg with a preferred dose of 100-1600 µg. The particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc).

25

30 For administration, the combination is suitably inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler (e.g. as sold under the trade mark Turbuhaler) or from a dry powder inhaler utilizing gelatine, plastic or other capsules, cartridges or blister packs.

35

A diluent or carrier, generally non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will give the medicament a desired taste, can be added to the powdered medicament.

5

Examples of the preparation of suitable dosage forms according to the invention include the following:

Formoterol fumarate dihydrate and budesonide (optionally premicronized) are mixed in the proportions given above.

10

The agglomerated, free-flowing micronized mixture may be filled into dry powder inhaler such as sold under the trade mark Turbuhaler. When a capsule system issued, it is desirable to include a filler in the mixture.

15

The micronized mixture may be suspended or dissolved in a liquid propellant mixture which is kept in a container that is sealed with a metering valve and fitted into a plastic actuator. The propellants used may be chlorofluorocarbons of different chemical formulae. The

20

most frequently used chlorofluorocarbon propellants are trichloromonofluoromethane (propellant 11), dichloro-difluoromethane (propellant 12),

dichlorotetrafluoroethane (propellant 114),

tetrafluoroethane (propellant 134a) and 1,1-difluoro-

25

ethane (propellant 152a). Low concentrations of a surfactant such as sorbitan trioleate, lecithin, disodium dioctylsulphosuccinate or oleic acid may also be used to improve the physical stability.

30

The invention is further illustrated by way of example with reference to the following Examples.

Example 1 - Dry Powder Inhaler (Turbuhaler)

35	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	200 µg

The storage unit of the inhaler is filled with sufficient for at least 200 doses.

	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	24 µg
	Budesonide	200 µg

The storage unit is filled with sufficient for at least 200 doses.

	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	100 µg

The storage unit is filled with sufficient for at least 200 doses.

15

Example 2 - Metered dose inhaler

	<u>Active ingredient</u>	<u>Per dose</u>
20	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	200 µg
	Stabilizer	0.1 - 0.7 mg
	Propellant	25 - 100 µl

25

	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	24 µg
	Budesonide	200 µg
	Stabilizer	0.1 - 0.7 mg
30	Propellant	25 - 100 µl

30

	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
35	Budesonide	200 µg
	Stabilizer	0.1 - 0.7 mg
	Propellant	25 - 100 µl

35

Example 3 - Metered dose dry powder formulation

	<u>Active ingredient</u>	<u>Per dose</u>
	Formoterol (as fumarate dihydrate)	12 µg
5	Budesonide	200 µg
	Lactose	up to 5, 12.5 or 25 mg
	<u>Active ingredient</u>	<u>Per dose</u>
10	Formoterol (as fumarate dihydrate)	24 µg
	Budesonide	200 µg
	Lactose	up to 5, 12.5 or 25 mg
	<u>Active ingredient</u>	<u>Per dose</u>
15	Formoterol (as fumarate dihydrate)	12 µg
	Budesonide	100 µg
	Lactose	up to 5, 12.5 or 25 mg

CLAIMS

1. A medicament containing, separately or together, (i) formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and (ii) budesonide for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.
2. A pharmaceutical composition for administration by inhalation in the treatment of respiratory disorder which comprises formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.
3. A pharmaceutical composition comprising effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.
4. Formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide for use in combination therapy by simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.
5. The use of formoterol (and/or a physiologically acceptable salt thereof) in the manufacture of a medicament for combination therapy where formoterol (and/or physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorder.
6. The use of budesonide in the manufacture of a medicament for combination therapy where formoterol

(and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorder.

5

7. The use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide in the manufacture of a medicament for combination therapy for simultaneous, sequential or separate administration of formoterol and budesonide by inhalation in the treatment of respiratory disorder.
- 10

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 92/02826

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/57; // (A61K31/57, 31:165)

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	ANNALS OF ALLERGY vol. 63, no. 3, September 1989, pages 220 - 224 JEAN H. MARSAC ET AL. 'Inhaled beta agonists and inhaled steroids in the treatment of asthma' cited in the application see page 221, column 2; table 1 see page 221, column 3, line 11 - line 15 * page 223; summary * ----	1-7
X	LUNG (USA) vol. 168, no. SUPP, 1990, NEW YORK pages 105 - 110 NILS SVEDMYR 'The current place of beta-agonists in the management of asthma' cited in the application see abstract -----	1-7

⁶ Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

⁷ "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention⁸ "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step⁹ "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents; such combination being obvious to a person skilled in the art.¹⁰ "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

07 APRIL 1993

Date of Mailing of this International Search Report

28/4/93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

LEHERTE C.F.M.